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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,421	09/08/2008	David Ray Filpula	213.1204-PCT-US	5480

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EXAMINER	
HISSONG, BRUCE D	

ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
01/19/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@lmiplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/590,421	FILPULA ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/20/2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55,57,58,61-75 and 77-109* is/are pending in the application.

4a) Of the above claim(s) *72,73 and 99-109* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55,57,58,61-71,74,75 and 77-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicants' response to the office action mailed on 9/7/2010 was received on 10/20/2010 and has been entered into the record.

2. Claims 55, 57-58, 61-75, and 77-109 are currently pending, with claims 72-73 and 99-109 withdrawn as non-elected subject matter. Claims 55, 57-58, 61-71, 74-75, and 77-98 are presently under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 55, 57-58, 61-71, and 80-95 remain rejected under 35 USC § 103(a) as being obvious in view of the combination of Drustrup (US 20030138403) and Durelli et al (The Lancet, 2002, Vol. 359, p. 1453-1460), as set forth on pages 4-6 of the office action mailed on 9/7/2010.

The claims of the present invention are drawn to a composition comprising IFN-β-1b conjugated to a polyalkylene oxide polymer having a molecular weight of at least about 12 kDa, and optionally, an excipient and a buffer, wherein the pH range of the solution is from about 3 to about 5. The claims also recite the claimed composition further comprising a surfactant, such as selected from poloxyethylene sorbitol esters and polyethylene glycol. The claims also recite the IFN-β-1b composition comprising a buffer, including sodium acetate, wherein the ionic strength is about 10 mM and the buffer is in a concentration of about 3-10 mM, and wherein the composition also comprises monosaccharides, disaccharides, and alditols, and specifically mannitol. Also recited are polyalkylene oxide polymer ranges from about 12 kDa to about 60 kDa, and more specifically, 30 kDa and 40 kDa, and wherein the

polyalkylene oxide polymer is conjugated to IFN-β-1b via the alpha-amino terminal of IFN-β-1b, or via an epsilon group of a lysine residue. The claims also recite a biologically-active polymer-IFN-β-1b conjugate wherein at least about 65 percent of the antiviral activity is retained relative to native IFN-β-1b, using the EMC/Vero or EMC/A549 antiviral assay, and wherein at least about 20 percent of the antiviral activity is retained. The claims also recite method of preparing the biologically active polymer-IFN-β-1b conjugate.

Drustrup teaches a formulation comprising IFN-β conjugated to polyethylene glycol having a molecular weight of 12 kDa, wherein said formulation also comprises an acetate buffer at 10 mM, and mannitol (an excipient), wherein the pH of said formulation is 5.5 (see Example 5). Furthermore, Drustrup teaches that the IFN of the formulation can be IFN-β or a variant thereof (paragraph 0022), formulations comprising IFN at 0.1 to 10 mg/ml (paragraph 0253), teaches pH ranges from 3.0 to 8.0, and teaches use of buffers such as acetate, succinate, citrate, and glycine at various ranges, such as 1-30 mM (paragraphs 0236-0254). Drustrup also teaches incorporation of polyethylene glycol into the formulations (paragraph 0243), and also teaches various methods of conjugation/attachment of various molecular weight PEG (e.g. 5 – 100 kDa PEG – paragraph 0207) to IFN-β polypeptides, including conjugation to the amino-terminus of IFN, and conjugation to lysine residues, which would necessarily involve an amide linkage (see paragraph 0040, 0386, see also the table between paragraphs 0037 and 0038, which describes attachment of various activated PEG molecules to various regions/residues). Furthermore, Drustrup discloses specific methods of preparing conjugates comprising IFN and PEG (see Examples 3 and 5, paragraph 0384-0386). Drustrup is silent regarding a composition comprising IFN-β-1b.

However, Durelli teaches that administration of IFN-β-1b is effective in treating multiple sclerosis. Specifically, Durelli compared administration of IFN-β-1a and IFN-β-1b, and showed that a higher percentage of individuals which received IFN-β-1b remained relapse-free compared with individuals receiving IFN-β-1a (51% vs 36%, see abstract and p. 1456, 1st – 2nd columns), and a higher percentage of patients which received IFN-β-1b remained free for development of new lesions compared to patients which are received IFN-β-1a (see Figure 3 and Table 5).

In the response received on 10/20/10, the Applicants argue that the claims are not obvious in view of the combination of Drustrup and Durelli because Durelli reports a clinical trail comparing administration of IFN-β-1a and IFN-β-1b for treatment of multiple sclerosis, wherein the IFN-β-1b was administered every other day and the IFN-β-1a was administered once a week. The Applicants assert that the disclosure of Durelli would not have taught or suggested the claimed invention because the disparity

in the dosing regimes (weekly vs every other day) used in the study would have made it impossible to draw any conclusions as to the relative potency of the two IFN-β analogs conjugated to a polyalkylene oxide such as PEG, and furthermore, a skilled artisan seeking a long-lasting conjugate would have looked to IFN-β-1a administered once per week rather than IFN-β-1b.

Furthermore, the Applicants argue that Pepinsky et al and Runkel et al show that IFN-β-1a antiviral activity is 10-fold higher than IFN-β-1b activity, and therefore a skilled artisan would know of the relative advantages of IFN-β-1a over IFN-β-1b for administration as a polymer conjugate, and it would have not have been expected that the less potent IFN-β-1b would have provided good kinetics and retention of potency when polymer conjugated, relative to IFN-β-1a. Additionally, the Applicants argue that the present invention provides a range of test data showing the advantages and disadvantages of various composition parameters. Specifically, the Applicants note that the claims require a pH ranging from pH 3.0 through pH 4.0, and the specification shows that compositions at these pH values did not exhibit aggregation, whereas compositions formulated at higher pH values showed aggregation, which would was not taught or suggested by the art of record and thus shows that the results of the instant invention are unexpected.

These arguments have been fully considered and are not persuasive. Regarding Applicants arguments that the results of Durelli and the relative differences in antiviral activity disclosed by Pepsinky and Runkel would point a person of skill in the art towards the conjugation of IFN-β-1a rather than IFN-β-1b, it is noted that Durelli clearly shows that administration of IFN-β-1b is clearly effective in treating multiple sclerosis and preventing relapses after treatment. Although a skilled artisan may be aware of the relative differences in antiviral activity between IFN-β-1a and IFN-β-1b, Durelli clearly provides a protocol in which administration of IFN-β-1b is effective in treating multiple sclerosis, and therefore a skilled artisan would have the motivation to create an IFN-β-1b-PEG conjugate regardless of the relative potency of IFN-b-1b in an antiviral assay.

The Applicants also argue that in view of Pepsinky and Runkel, it would not have been expected that the less potent IFN-β-1b would have provided good kinetics and retention of potency when conjugated, relative to IFN-β-1a. However, the Durelli study shows that the relatively low potency of IFN-b-1b can be overcome with more frequent dosing. It is also noted that the claims do not require any specific level of potency relative to IFN-β-1a or any other IFN.

Regarding Applicants arguments that the instant invention provides for unexpectedly superior results because IFN-β-1b formulated by the present invention exhibited lower aggregation, it is noted that

Drustrup teaches formulation at a pH range (3.0 to 8.0) which overlaps with the presently claimed range, and via routine optimization, and skilled artisan would be able to determine the most effective pH.

2. Claims 74, 77-79, and 96-98 remain rejected under 35 USC § 103(a) as being obvious in view of the combination of Drustrup (US 20030138403), Durelli et al (The Lancet, 2002, Vol. 359, p. 1453-1460), and McManus et al (US 20070166277), as set forth on pages 7-8 of the office action mailed on 9/7/2010.

In the response received on 10/20/2010, the Applicants argue that the claimed subject matter is not obvious over the cited combination because, for the reasons discussed above, Drustrup and Durelli do not provide the motivation to create the claimed IFN-β-1b conjugate, and the disclosure of McManus does not remedy the deficiencies of Drustrup and Durelli.

These arguments have been fully considered and are not persuasive. As discussed above, the combination of Drustrup and Durelli does provide the motivation to create an IFN-β-1b conjugate as currently claimed, and therefore the rejection is maintained for reasons of record set forth in the previous office action.

3. Claims 75 remains rejected under 35 USC § 103(a) as being obvious in view of the combination of Drustrup (US 20030138403), Durelli et al (The Lancet, 2002, Vol. 359, p. 1453-1460), and Saifer et al (US 20040126361), as set forth on pages 8-9 of the office action mailed on 9/7/2010.

In the response received on 10/20/2010, the Applicants argue that the claimed subject matter is not obvious over the cited combination because, for the reasons discussed above, Drustrup and Durelli do not provide the motivation to create the claimed IFN-β-1b conjugate, and the disclosure of Saifer does not remedy the deficiencies of Drustrup and Durelli.

These arguments have been fully considered and are not persuasive. As discussed above, the combination of Drustrup and Durelli does provide the motivation to create an IFN-β-1b conjugate as currently claimed, and therefore the rejection is maintained for reasons of record set forth in the previous office action.

Conclusion

No claim is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571)272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bruce D. Hissong
Art Unit 1646

/Robert Landsman/
Primary Examiner, Art Unit 1647